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(54) READILY SOLUBLE HARD GELATIN CAPSULE

(57)Abstract:
PURPOSE: To obtain a readily soluble hard gelatin capsule completely preventing insolubilization phenomena caused by change with time.
CONSTITUTION: This readily soluble hard gelatin capsule comprises 70-100wt.% of succin-gelatin as a base. The capsule is produced by reacting gelatin with succinic anhydride by a conventional procedure to produce succin-gelatin, properly blending the succin-gelatin with an ordinary gelatin in the range of the blending ratio, optionally adding a coloring matter, a shading agent, etc., to prepare a gelatin solution and molding and processing by a conventional procedure. The readily soluble hard gelatin capsule has more excellent solubility and disintegration than those of an ordinary hard capsule and the characteristics are shown especially noticeably when the capsule is preserved under a severe condition for a long period of time.

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* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the soluble hard gelatine capsule which makes amber-ized gelatin an indispensable constituent in more detail about a soluble hard gelatine capsule.
[0002]
[Description of the Prior Art] The soluble soft capsule which made soluble give a capsule is already known by processing gelatin from an organic acid, amino acid, etc., and acylating the amino group in gelatin. For example, the soft capsule which added the polypeptide into gelatin is indicated by the soft capsule which blended amino acid, the soluble soft capsule which makes an indispensable constituent modification DOZERACHIN which processed and obtained gelatin by the organic acid to No. 106876 [50 to] in No. 4267 [57 to], and a JP,58-103316,B list at a JP,55-32382,B list, and JP,58-62120,B at JP,57-30088,B.
[0003] First of all, they are that, as for research of a large number which are going to make a gelatin soft capsule easily dissolvable having been made, the thickness of the wall of a soft capsule is physically applied to dissolution by time amount comparatively thickly (about 5 or more times of a hard filled capsule), and the shape of that the contents of a soft capsule are usually liquefied, or mud. Therefore, a chemical change tends to happen between contents and a capsule, and a possibility that a capsule insolubilizes by it is based on the reasons of a high thing and a soft capsule having many which expect collapsibility instancy (for example, a baths soft capsule, the soft capsule for antibacterials).
[0004] However, most attempts in which the above-mentioned easily dissolvable-ized technology applied to the soft capsule is applied also to a hard filled capsule until now from the reasons of that a hard gelatine capsule does not almost have a possibility that a capsule insolubilizes by the interaction with contents since the thing with the thickness of the wall comparatively thin [like] mentioned already and contents are usually particulate matters, being unable to consider probably the use which expected collapsibility instancy are not made.

[0005]
[Objects of the Invention] However, for this invention persons, a hard filled capsule is also solubility by aging, When a hard filled capsule is filled up with a certain kind of drug, for example, a macrolide etc., collapsibility falls in many cases It notes that a hard filled capsule also has the utility made easily dissolvable since a hard filled capsule insolubilizes as a result of a chemical change. The amber-ized gelatin which the succinic anhydride conventionally used only for easily dissolvable-ization of a soft capsule is made to react to gelatin as a result of examining the manufacturing method of an easily dissolvable-ized hard filled capsule, and is obtained, Or when using as a material what blended gelatin usual at 0 - 50% of the weight of a rate with this amber-ized gelatin, it finds out that a soluble hard gelatine capsule can be manufactured, and came to complete this invention.
[0006] That is, this invention offers the soluble hard gelatine capsule which becomes considering 70 - 100% of the weight of amber-ized gelatin as a capsule basis.
[0007] What is necessary is to make a succinic anhydride react to gelatin according to a conventional method first, to manufacture amber-ized gelatin, to mix this amber-ized gelatin

and usual gelatin suitably within the limits of the above-mentioned rate of a compounding ratio, to add a coloring agent, a protection-from-light agent, etc. if needed, to prepare a gelatin solution, and just to carry out fabrication henceforth, according to a general formula, as a conventional method, in order to manufacture the soluble hard gelatine capsule of this invention.

[0008]

[Effect of the Invention] Since the amino group of the amino acid which is the constituent of gelatin which processes gelatin by the succinic anhydride is blocked (acylation), therefore the inquiry of yin-and-yang both the ion between molecules decreases and a water molecule becomes easy to trespass upon the interior of gelatin, collapsibility is improved. The insolubilization phenomenon which it becomes impossible for the atomic group in an encapsulation object (for example, aldehyde group) to combine with this therefore, and originates in the chemical bond of a capsule and packing by the blockade of this amino group on the other hand can be prevented. So, if only the point of easily-dissolvable-izing of a capsule is noted, the rate of combination of amber-ized gelatin is so desirable that it is high. However, if the content of amber-ized gelatin becomes high, the rate of combination of amber-ized gelatin should be chosen according to the existence of the atomic group which the titanium oxide usually added by the gelatin solution as a protection-from-light agent condenses, an irregular color arises, or there is orientation for a capsule to crack-come to be easy, therefore is easy to combine with the property of an encapsulation object, especially the amino group, its number, and its activity.

[0009] Although the easily dissolvable-ized hard gelatine capsule concerning this invention is excellent in solubility and collapsibility as compared with the usual hard gelatine capsule, this feature appears notably especially, when a capsule is saved under abuse conditions for a long period of time.

[0010] When the macrolide shown in the trial 1 is used for the soluble hard gelatine capsule concerning this invention as packing, a very good result is obtained. An example is given to below and this invention is further explained to details.

[0011] 300l. of phosphate buffers is added to example 1 gelatin 5.9kg, and it dissolves at 40 degrees C after 1-hour swelling. 11.8kg of powder-like succinic anhydrides is added in small quantity [every] 90 minutes, keeping this liquid at ph8.0 by 10-N sodium hydroxide, and it agitates at 40 degrees C for 20 hours. Distilled water was added to this, and it was referred to as 600l., and, subsequently dialyzed, filtered and dried.

[0012] Swelling of amber-ized gelatin 3.5kg and the non-amber-ized gelatin 3.5kg obtained in the top was put in and carried out to 14l. of distilled water, and it heated at 60 degrees C under churning, and was made to dissolve completely. 975ml (21.8 % of the weight) of titanium oxide water dispersions was added to this solution, it agitated until it became homogeneity, and degassing processing was carried out with the conventional method. The obtained gelatin solution was taught to the capsule manufacturing installation, and was cast to the capsule of size No. 0.

[0013] According to the method indicated in the trial 1 example 1, the decay action of 11 sorts of No. 0 gelatine capsules (cap: a pink opaque, a body:White opaque, packing:macrolide) which were made to increase by a unit of 10%, and manufactured amber-ized gelatin content until it resulted to 100% from 0% was observed according to the method of examining a publication to the tenth amendment (1981) of a Japanese pharmacopoeia. That is, time amount (A) until a capsule carries out a opening from test initiation about each capsule left for one month at the capsule left for ten days and 40 degrees C, and 75% of relative humidity with the capsule immediately after manufacture, 60 degrees C, and 75% of relative humidity, time amount (B) until contents medicine flows out, and time amount (C) until decay of a capsule is completed were measured. A result is shown in the following table 1. In addition, each data in a table is the average of six capsules.

[0014]

[A table 1]

ゼラチン溶液 測定		コハク化ゼラチン / 普通のゼラチン										
		100% / 0%	90% / 10%	80% / 20%	70% / 30%	60% / 40%	50% / 50%	40% / 60%	30% / 70%	20% / 80%	10% / 90%	0% / 100%
		分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒
製造直後	A	52	1 03	1 15	1 44	1 02	55	55	1 01	1 08	1 01	1 06
	B	3 08	3 15	3 22	3 48	3 22	3 08	2 27	3 03	3 32	2 19	3 13
	C	5 46	5 40	5 35	5 42	5 48	5 43	5 58	6 20	6 15	6 21	6 08
10日目 60℃ RH75%	A	43	35	56	1 47	1 44	5 03	開口せず	開口せず	開口せず	開口せず	開口せず
	B	3 14	4 23	4 44	4 38	5 58	6 12	—	—	—	—	—
	C	5 24	8 37	9 21	8 28	10 14	不溶膜が残った	—	—	—	—	—
1カ月目 40℃ RH75%	A	51	—	—	—	—	1 31	—	—	—	—	2 00
	B	3 14	—	—	—	—	3 48	—	—	—	—	5 03
	C	5 55	—	—	—	—	7 23	—	—	—	—	不溶膜が残った

[0015] Although the improvement of clear collapsibility is observed from the hard gelatine capsule which contains amber-ized gelatin 60% of the weight so that clearly from a table 1, it turns out that the orientation will become remarkable if content becomes 70% of the weight or more, and the insolubilization phenomenon by aging is prevented completely.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[Industrial Application] This invention relates to the soluble hard gelatine capsule which makes amber-ized gelatin an indispensable constituent in more detail about a soluble hard gelatine capsule.

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PRIOR ART

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EFFECT OF THE INVENTION

[Effect of the Invention] Since the amino group of the amino acid which is the constituent of gelatin which processes gelatin by the succinic anhydride is blocked (acylation), therefore the inquiry of yin-and-yang both the ion between molecules decreases and a water molecule becomes easy to trespass upon the interior of gelatin, collapsibility is improved. The insolubilization phenomenon which it becomes impossible for the atomic group in an encapsulation object (for example, aldehyde group) to combine with this therefore, and originates in the chemical bond of a capsule and packing by the blockade of this amino group on the other hand can be prevented. So, if only the point of easily-dissolvable-izing of a capsule is noted, the rate of combination of amber-ized gelatin is so desirable that it is high. However, if the content of amber-ized gelatin becomes high, the rate of combination of amber-ized gelatin should be chosen according to the existence of the atomic group which the titanium oxide usually added by the gelatin solution as a protection-from-light agent condenses, an irregular color arises, or there is orientation for a capsule to crack-come to be easy, therefore is easy to combine with the property of an encapsulation object, especially the amino group, its number, and its activity.

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		分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒
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	B	3 08	3 15	3 22	3 48	3 22	3 08	2 27	3 03	3 32	2 19	3 13
	C	5 46	5 40	5 35	5 42	5 48	5 43	5 58	6 20	6 15	6 21	6 08
10日目 60℃ RH75%	A	43	35	56	1 47	1 44	5 03	開口せず	開口せず	開口せず	開口せず	開口せず
	B	3 14	4 23	4 44	4 38	5 58	6 12	–	–	–	–	–
	C	5 24	8 37	9 21	8 28	10 14	不溶膜が残った	–	–	–	–	–
1カ月目 40℃ RH75%	A	51	–	–	–	–	1 31	–	–	–	–	2 00
	B	3 14	–	–	–	–	3 48	–	–	–	–	5 03
	C	5 55	–	–	–	–	7 23	–	–	–	–	不溶膜が残った

[0015] Although the improvement of clear collapsibility is observed from the hard gelatine capsule which contains amber-ized gelatin 60% of the weight so that clearly from a table 1, it turns out that the orientation will become remarkable if content becomes 70% of the weight or more, and the insolubilization phenomenon by aging is prevented completely.

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(54)【発明の名称】　易溶性硬質ゼラチンカプセル

(57)【要約】
【目的】　易溶性硬質ゼラチンカプセルを提供する。
【構成】　７０～１００重量％のコハク化ゼラチンをカプセル基剤とするカプセルは、易溶性硬質ゼラチンカプセルとして優れている。

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【特許請求の範囲】
【請求項１】　７０～１００重量％のコハク化ゼラチンをカプセル基剤としてなる易溶性硬質ゼラチンカプセル。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は、易溶性硬質ゼラチンカプセルに関し、更に詳しくは、コハク化ゼラチンを必須構成成分とする易溶性硬質ゼラチンカプセルに関する。
【０００２】
【従来技術】ゼラチンを有機酸、アミノ酸などで処理し、ゼラチン中のアミノ基をアシル化することによって、カプセルに易溶性を付与せしめた易溶性軟カプセルは既に知られている。例えば特公昭５７－３００８８号には、アミノ酸を配合した軟カプセル、特公昭５５－３２３８２号並びに５７－４２６７号および特公昭５８－１０３３１６号並びに５０－１０６８７６号には、ゼラチンを有機酸で処理して得たモディファイドゼラチンを必須構成成分とする易溶性軟カプセル、特公昭５８－６２１２０号には、ゼラチンにポリペプチドを添加した軟カプセルが開示されている。
【０００３】そもそも、ゼラチン軟カプセルを易溶化しようとする多数の研究がなされて来たのは、軟カプセルの壁の厚さが比較的厚く(硬カプセルの約５倍以上)、物理的に溶解に時間がかかること、軟カプセルの内容物は通常液状または泥状であり、従って内容物とカプセルとの間で化学変化が起こり易く、それによってカプセルが不溶化する可能性が高いこと、軟カプセルには、即時崩壊性を期待しているものが多いこと(例えば浴用剤軟カプセル、消毒液用軟カプセル)、などの理由による。
【０００４】しかるに硬質ゼラチンカプセルは、既述した様にその壁の厚さが比較的薄いこと、内容物が通常粉粒体である為、内容物との相互作用によってカプセルが不溶化する可能性がほとんどないこと、および即時崩壊性を期待した用途はまず考えられないこと、などの理由から、これまで、軟カプセルに適用した上記の易溶化技術を硬カプセルにも応用するという試みは、ほとんどなされていない。
【０００５】
【発明の目的】しかしながら、本発明者らは、硬カプセルも経時変化によって溶解性、崩壊性が低下することが多いこと、また、ある種の薬物、例えばマクロライド系抗生物質などを硬カプセルに充填した場合には、化学変化の結果硬カプセルが不溶化すること、などから、硬カプセルも易溶化する実益のあることに着目し、易溶化硬カプセルの製造法について検討した結果、ゼラチンに、従来軟カプセルの易溶化にしか使用されたことのない無水コハク酸を反応させて得られるコハク化ゼラチン、またはこのコハク化ゼラチンに０～５０重量％の割合で通常のゼラチンを配合したものを材料として使用すれば、

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易溶性硬質ゼラチンカプセルを製造することができることを見い出し本発明を完成するに至った。
【０００６】即ち本発明は、７０～１００重量％のコハク化ゼラチンをカプセル基剤としてなる易溶性硬質ゼラチンカプセルを提供するものである。
【０００７】本発明の易溶性硬質ゼラチンカプセルを製造するには、先ず常法に従ってゼラチンに無水コハク酸を反応させてコハク化ゼラチンを製造し、このコハク化ゼラチンと通常のゼラチンを上記の配合比率の範囲内で適宜混合し、以降、一般的な処方に従い、必要に応じて着色剤、遮光剤などを添加してゼラチン溶液を調製し、常法通り成形加工すればよい。
【０００８】
【発明の効果】ゼラチンを無水コハク酸で処理するゼラチンの構成成分であるアミノ酸のアミノ基が封鎖(アシル化)され、従って分子間の陰陽両イオンの引き合いが減少し、水分子がゼラチン内部に侵入し易くなる為、崩壊性が改善される。一方、このアミノ基の封鎖により、カプセル充填物中の原子団(例えばアルデヒド基)がこれと結合できなくなり、従って、カプセルと充填物との化学結合に起因する不溶化現象を防止することができる。それ故、カプセルの易溶化という点にのみ着目すれば、コハク化ゼラチンの配合率は高い程望ましい。しかしながら、コハク化ゼラチンの含有率が高くなると、通常遮光剤としてゼラチン溶液に添加される酸化チタンが凝集したり、色むらが生じたり、あるいはカプセルが割れ易くなる傾向があり、従って、カプセル充填物の性質、特にアミノ基と結合し易い原子団の有無、その数、およびその活性度に応じてコハク化ゼラチンの配合率を選択すべきである。
【０００９】本発明に係る易溶化硬質ゼラチンカプセルは、通常の硬質ゼラチンカプセルに比較して溶解性、崩壊性に優れているが、この特徴は、カプセルを長期間、虐待条件下で保存した場合に特に顕著にあらわれる。
【００１０】本発明に係る易溶性硬質ゼラチンカプセルは、例えば試験１に示したマクロライド系抗生物質を充填物として使用した場合、極めて良好な結果が得られる。以下に実施例を挙げて本発明を更に詳細に説明する。
【００１１】実施例１
ゼラチン５．９kgにリン酸塩緩衝液３００lを加え、１時間膨潤後４０℃で溶解する。この液を１０N水酸化ナトリウムでph８．０に保ちながら粉末状の無水コハク酸１１．８kgを少量ずつ９０分で添加し、４０℃で２０時間撹拌する。これに蒸留水を加えて６００lとし、次いで透析、ろ過、乾燥した。
【００１２】上で得たコハク化ゼラチン３．５kgおよび非コハク化ゼラチン３．５kgを蒸留水１４lに入れて膨潤させ、撹拌下６０℃に加熱して完全に溶解させた。この溶液に酸化チタン水分散液(２１．８重量％)９７５ml

を加え、均一になるまで撹拌し、常法により脱泡処理した。得られたゼラチン溶液をカプセル製造装置に仕込み、サイズ０号のカプセルに成型した。

【００１３】試験１

実施例1に記載した方法に従い、コハク化ゼラチン含有率を０％から１００％に至るまで１０％づつ増加させて製造した１１種の０号ゼラチンカプセル(キャップ:ピンクオペイク、ボディ:ホワイトオペイク、充填物:マクロライド系抗生物質)の崩壊挙動を、日本薬局方第十改正(１９８１)に記載の試験法に準じて観察した。即ち、製造直後のカプセル、６０℃、相対湿度７５％で１０日間放置したカプセル、および４０℃、相対湿度７５％で１ケ月間放置した各カプセルにつき、試験開始からカプセルが開口するまでの時間(A)、内容薬が流出するまでの時間(B)、およびカプセルの崩壊が完了するまでの時間(C)を測定した。結果を以下の表１に示す。尚、表中の各データはカプセル６個の平均値である。

【００１４】

【表１】

ゼラチン溶液 測定		コハク化ゼラチン / 普通のゼラチン 100% 0%	90% 10%	80% 20%	70% 30%	60% 40%	50% 50%	40% 60%	30% 70%	20% 80%	10% 90%	0% 100%
		分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒	分 秒
製造直後	A	52	1 03	1 15	1 44	1 02	55	55	1 01	1 08	1 01	1 06
	B	3 08	3 15	3 22	3 48	3 22	3 08	2 27	3 03	3 32	2 19	3 13
	C	5 46	5 40	5 35	5 42	5 48	5 43	5 58	6 20	6 15	6 21	6 08
10日目 60℃ RH75%	A	43	35	56	1 47	1 44	5 03	開口せず	開口せず	開口せず	開口せず	開口せず
	B	3 14	4 23	4 44	4 38	5 58	6 12	−	−	−	−	−
	C	5 24	8 37	9 21	8 28	10 14	不溶膜が残った	−	−	−	−	−
1カ月目 40℃ RH75%	A	51	−	−	−	−	1 31	−	−	−	−	2 00
	B	3 14	−	−	−	−	3 48	−	−	−	−	5 03
	C	5 55	−	−	−	−	7 23	−	−	−	−	不溶膜が残った

【００１５】表１から明らかな様に、コハク化ゼラチンを６０重量％含有する硬質ゼラチンカプセルから、明瞭な崩壊性の改善が観察されるが、含有率が７０重量％以上になるとその傾向が顕著になり、経時変化による不溶化現象が完全に防止されることがわかる。